



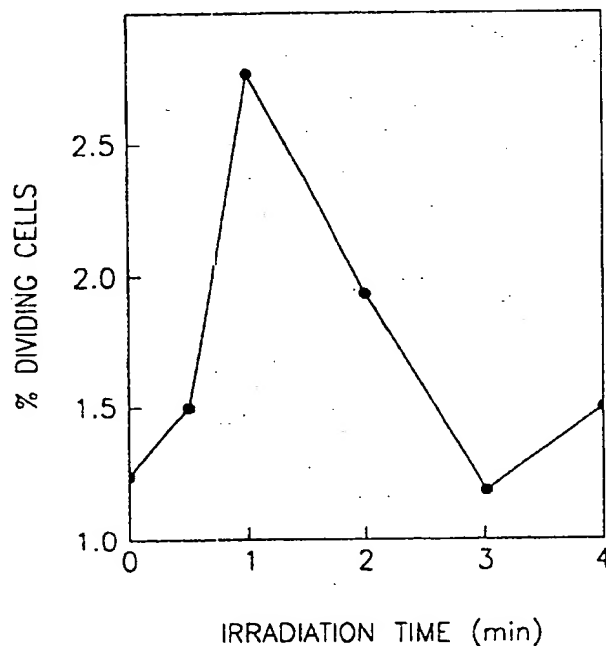
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification 6.: A61N 5/06 | A1 | (11) International Publication Number: WO 98/23329 (43) International Publication Date: 4 June 1998 (04.06.98) |
| (21) International Application Number: PCT/IL97/00375 (22) International Filing Date: 18 November 1997 (18.11.97) (30) Priority Data: 119683 25 November 1996 (25.11.96) IL (71)(72) Applicant and Inventor: LUBART, Rachel [IL/IL]; Han-kin Street 10, 62506 Tel Aviv (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |

(54) Title: **DEVICE FOR LIGHT IRRADIATION ONTO TISSUE**

(57) Abstract

A method and device for inducing or promoting growth and proliferation of skin cells or tissue or for controlling bacterial skin infection is described. The skin cells are irradiated with a low-intensity broad spectrum light at a wavelength of between about 340 to 3,000 nm. The increase in rate of cultivated cells is useful for example to obtain skin-like tissue needed for skin grafts or for promoting healing of skin wounds or lesions. Light-induced skin bacteria control is useful for example in the treatment of bacterial infections of the skin.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|------------------------------------------|----|----------------------------------------------|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |



DEVICE FOR LIGHT IRRADIATION ONTO TISSUE

FIELD OF THE INVENTION

The present invention concerns a method and device for affecting growth and proliferation of cells or tissue by light irradiation. The device and method of the invention are useful in increasing the rate of growth and proliferation of skin epithelial cells. Another use of the inventive device and method is the controlling bacterial infections of the skin, e.g. in the case of *acne vulgaris*. The device and method of the invention may thus be employed in the treatment of skin, oral or vaginas wounds or lesions, as well as irradiating keratinocytes in culture to increase the yield of the culture.

10 In the following, irradiation of light intended to increase rate of growth and proliferation of cells will be referred to herein at times as "*light-induced growth acceleration*"; treatment for the purpose of control of bacterial infections will be referred to herein at times as "*light-induced bacteria control*"; treatment of skin or oral wounds or lesions by light
15 irradiation for the purpose of accelerating healing, will be referred to herein at times as "*light therapy*".

LIST OF PRIOR ART

The following is a list of prior art considered to be relevant as a background to the invention:

- 5 1. Mester, E.: Clinical results of laser stimulation and experimental studies on the mechanism of action *Minerva Med.*, 72:2195-2199 (1981).
- 10 2. Lyons R.F., Abergel, R.P., White, R.A., Dwyer R.M., Castel, J.C., Uitto, J.: Biostimulation of wound healing *in vivo* by Helium-neon laser, *Ann. Plast. Surg.*, 18:47-50 (1987).
- 15 3. Surinchak, J.S., Alago, M.L., Bellamy R.F., Stuck, B.E., Belkin, M.: Effects of low-level energy lasers on the healing of full-thickness skin defects, *Lasers Surg. Med.*, 2:267-274 (1983).
4. Chavrier, C., Hartmann, D., Couble M.L., Msloire H.: Laser a infra-rouge et cicatrisation conjonctive en chirurgie parodontale, *J. Parod.*, 5:209-212 (1986).
- 20 5. Lubart R., Wollman, Y, Friedman, H: Effects of visible and near IR lasers on cell cultures, *J. Photochem. Photobiol. B. Biol.*, 12:305-311 (1992).
- 25 6. Lubart, R., Friedman, H., Peled, I, Grossman, N: Light effect on fibroblast proliferation, *Laser Therapy*, 5:55-57 (1993).
7. Grossman, N., Reuveni, H., Halevy, S., Lubart, R: Visible light promotes proliferation of normal skin cells, *J. Invest. Dermatol.*, 102:649A (1994).
- 30 8. Kjeldstad B., Photoinactivation of propionibacterium acnes by near UV light, *Z. Naturforsch* 39(C):300-302 (1984).
- 35 9. Relø, T.B., Reisaeter G., and Johnson, A., Photodestruction of propionibacterium acnes porphyrins, *Z. Naturforsch*, No. C 125-128 (1985).

40 The above prior art documents will be referred to in the text by indicating their numbers from the above list within brackets. It should be noted that the acknowledgement of these references herein does not amount

to an indication that these are by any way relevant to the issue of patentability of the appended claims.

BACKGROUND OF THE INVENTION

5 Light therapy using low energy visible or near infrared light sources has been known to have a beneficial biological effect on a variety of tissues. Thus, during the last decade, low energy lasers (LEL) were introduced in treatment of wounds or lesions in a variety of tissue. LEL (mainly He-Ne lasers) has been proven effective in patients in promoting
10 epithelization in full thickness skin defects, as well as for gynecological problems and lesions in oral epithelia^(1,2,3,4).

 In treatment of acute massive burn wounds, particularly such that cover large portions of the body area, it is necessary to bring to regrowth of skin over the burnt area, the standard medical practice of grafting of
15 autologous tissue is very often complicated by the relative shortage of autologous donor sites. A primary advance towards this problem has been the development of an *in vitro* cultivation technique for human epidermal keratinocytes. The main disadvantage of such cultivation methods is that it requires a period of three to six weeks to obtain sufficiently large quantities
20 of cultured tissue ready for grafting.

 Studies with skin derived cultured cells (normal human fibroblasts and keratinocytes) showed that irradiation of visible, near infrared or near ultraviolet (UVA) light at low energy densities, was effective in promoting proliferation of the cells; against this, irradiation at higher energy densities
25 inhibited cell growth^(5,6,7). Light in the UVA and in the visible light range was found to destroy bacteria such as *Propionibacterium acnes*^(8,9). Radiation sources used hitherto included a variety of monochromatic and non-monochromatic light sources, irradiated at a wavelength of 360 nm (UVA), 540 nm and 600-900 nm, as well as HeNe 632 nm lasers and 780 nm diode
30 lasers. It should be noted that similar light sources are used for selective destruction of tumors by photoactivation of sensitizing drugs, in a technique known as photodynamic therapy (PDT).

A common-problem associated with all prior art used light sources is that they are relatively complicated and expensive, and not readily available to physicians.

5 SUMMARY OF THE INVENTION

It is the object of the invention to provide a method and device for light induced growth modulation of skin or epithelial cells.

It is an object in accordance with one embodiment of the invention to provide such a method and device for light-induced growth
10 acceleration of skin or epithelial cells, such as fibroblasts and keratinocytes, in culture.

It is an object in accordance with another embodiment of the invention to provide a method and device for light-induced bacteria control on the skin as an epithelium, e.g. and or vaginal epithelium.

15 It is an object in accordance with a further embodiment of the invention to provide a method and device useful in light therapy of wounds or lesions.

The present invention provides, by a first of its aspects, a method of inducing or promoting growth and proliferation of skin cells or tissue or
20 for controlling bacterial skin infection, comprising irradiating the skin cells with a low-intensity broad spectrum light at a wavelength between about 340 to 3,000 nm.

The present invention provides, by another of its aspects, a device for use in promoting or inducing growth and proliferation of skin cells or
25 for controlling bacterial skin infection, the device comprising a light source which comprises a lamp emitting a broad spectrum light at a wavelength between about 360 to 3,000 nm. The device may further comprise a focusing assembly as well as a light filtration assembly.

30 For some uses, e.g. irradiation onto wounds or lesions within the mouth or vaginas, the device may be equipped with a fiber optic so as to deliver the light to the desired site.

In accordance with one embodiment, the method and device are used for light-induced growth acceleration cells, e.g. skin cells, in culture, i.e., to induce or promote growth and proliferation of these cells. The device and method in accordance with this embodiment are particularly
5 useful in increasing the rate of cultivation of such cells in order to rapidly obtain skin-like tissue for grafting onto burn wounds. The device in accordance with this embodiment may comprise a lens adapted to diffuse the light onto the entire surface of the culture, or means to move the light skin, periodically across the culture.

10 In accordance with another embodiment, the method and device are used for light-induced skin bacteria control. Skin bacteria control includes destruction of bacterial cells, as well as arresting growth and proliferation of the bacteria. It was found in accordance with the invention that the destruction of bacteria by light irradiation is improved in an oxygen
15 rich environment; accordingly by a preferred embodiment of the invention the bacteria skin control is a combined irradiation and oxygen flows into the skin. By another preferred embodiment the oxygen is supplied as a peroxide, e.g. H_2O_2 .

20 In accordance with another embodiment of the invention, the method and device are utilized for light therapy of skin as epithelium for inducing or promoting healing of skin wounds or lesions.

DETAILED DESCRIPTION OF THE INVENTION

25 Unlike the prior art, the present invention utilizes a light source, which is not coherent and not polarized and is capable of irradiating relatively large tissue areas. In order to induce a positive, i.e. a regeneration stimulating effect on the skin or epithelium, the light intensity should preferably be below about 800 mW/cm^2 . It is clear however that for effective light therapy, the light intensity cannot be too low since otherwise
30 there will likely be no effect. Typically, a lower limit of light intensity

- 6 -

would be about 1 mW/cm². A preferred range of light intensity is 10-200 mW/cm².

The light source used in accordance with this invention emits, a "white" light, i.e. a light source emitting light of a broad spectrum covering the entire visible and optionally also the near infrared spectrum. An example of such a light source is a halogen lamp which emits light at wavelengths within the range of 340 to 3,000 nm. In order to avoid heating of the target, the IR portions of the emitted light may typically be filtered out so as to obtain light irradiation on the target at a wavelength within the range of about 340 to 1,200 nm, preferably within the range of about 340 to 800 nm.

In addition, the light may also be filtered through a UV filter for filtering out this harmful portion of the spectrum, thereby increasing safety.

The device in accordance with the invention may typically also comprise a lens for focusing the light onto the target cells or tissue.

Light may be irradiated either continuously or in pulses. Continuous light irradiation will typically be preferred in lower light intensities while pulsed irradiation will be preferred in higher light intensities. The decision whether to use constant irradiation or pulsed light irradiation depends on the exact application and on the total desired irradiation.

It will no doubt be clear to the artisan that the effect of the light depends both on the light intensity as well as on the duration of irradiation. In other words, high intensity irradiation requires a lower duration than a low intensity irradiation. Clearly, when depending on the duration of a pulsed light the net light time should be factored.

The effect of irradiation may at times be enhanced by the addition of photosensitizer substances to the target cells or tissue. For example, a culture of fibroblasts or keratinocytes may be supplemented with small amounts of a photosensitizer substance, such as hematoporphyrin derivatives prior to light irradiation. Such substances may also be applied topically onto the skin prior to the light therapy. The concentration of such substance is

typically substantially lower than concentrations used in photodynamic therapy.

The invention will be illustrated further by the following examples:

5

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a schematic representation showing the percent of dividing fibroblast cells following their irradiation with a light source consisting of a 40 mW/cm² halogen lamp.

10

Fig. 2 is a schematic representation showing the optical density (OD) at 660 nm of propionibacterium acne cultures at various periods of time following their irradiation with a light source at 550 mW/cm² for 90 mins. The OD of the irradiated cultures was compared to a similar culture which was not subjected to irradiation.

15

Example 1

3T3 NIH fibroblast cells were seeded in 25 or 96 multi-well plates. The concentration of cells was about $2.5 \times 10^3 - 10^4$ cells/well, respectively. 48 hours later cells were washed and exposed to light from a light source consisting of a 40 mW/cm² halogen lamp for various periods of time (in triplicate) while in the phosphate buffered saline (PBS). Following irradiation, the cultures were replenished with fresh growth media and were further incubated for 24-72 hours. At the end of the incubation, the cultures were washed with PBS and trypsinized.

25

Fig. 1 shows the percent of proliferating cells that were divided 24 hours after irradiation. As can be seen, the number of dividing cells peaked in the culture which had been previously irradiated with the light source for 1 min.

30

This experiment demonstrates that irradiation of keratinocytes with light emitted from a halogen lamp accelerates growth and proliferation of these cells. This may be useful in growing tissue for skin grafts, wherein

appropriate irradiation of the cells may result in a decrease in the time required to obtain a specific amount of such *in vitro* growth tissue.

Example 2

5 17 young individuals who had adolescent wounds were treated by irradiation of their facial skin, using a device in accordance with the invention. The treatment of each individual consisted of three irradiations per week, each one with a light intensity of 40 mW/cm² for two minutes on the infected area.

10 The tested individuals reported dramatic improvement in their facial conditions and examination of the individuals showed that after this treatment, their faces had no wounds and no scars.

 This clearly demonstrates the beneficial effect of irradiation with a halogen lamp on the treatment of skin wounds or lesions.

15

Example 3

 Individuals with adolescent wounds were treated by irradiating their facial skin similarly as in Example 2. A 2-3% H₂O₂ solution was applied onto the skin shortly before the irradiation.

20 A marked improvement in the individual's condition was observed.

Example 4

25 50 individuals who had Herpes on their lip were treated twice or three times a day with the light source as described above. Each treatment was at 120 mW/cm² for 2 mins. Two to three days after beginning of the treatment, a significant improvement (decrease in severity of infection) was observed.

Example 5

30 Cultures of propionibacterium acnes were irradiated with the light source described above at 550 mW/cm² for 90 mins. As seen in Fig. 2,

irradiation of the cells resulted in inhibition of their growth as compared to no-irradiated control cells.

CLAIMS:

1. A method of inducing or promoting growth and proliferation of cells or tissue, comprising irradiating the cells with a low-intensity broad spectrum light at a wavelength between about 340 to 3,000 nm.
2. A method for controlling bacterial infections of skin or epithelium comprising irradiating the skin or epithelium with a low-intensity broad spectrum light at a wavelength between about 340 to 3,000 nm.
3. A method according to Claim 1 or 2, wherein the wavelength of the light is between about 340 to 1,200 nm.
4. A method according to Claim 1, 2, or 3, wherein the light irradiation is at a light intensity of below about 800 mW/cm².
5. A method according to Claim 4, wherein the light intensity is at a range of about 10 to 200 mW/cm².
6. A method according to Claim 1, comprising irradiating cultured skin cells.
7. A method according to Claim 1 or 2, for treatment of skin in order to induce or promote healing of skin wounds and lesions comprising irradiating the skin with said light.
8. A method according to any one of Claims 1-7, wherein the effect of light is enhanced by photosensitizer substances.
9. A method according to Claim 7, comprising applying oxygen or a peroxide solution onto the skin.
10. A device for use in promoting or inducing growth and proliferation of skin cells or for controlling bacterial infections of the skin, the device comprising a light source which comprises a lamp emitting a broad spectrum light at a wavelength between about 340 to 3,000 nm.
11. A device according to Claim 10, comprising a focusing assembly.
12. A device according to Claim 10 or 11, comprising a light filtration assembly.
13. A device according to Claim 10, comprising a fiber optic.

14. A device according to Claim 8, for use in the method according to any one of Claims 1-7.

1/2

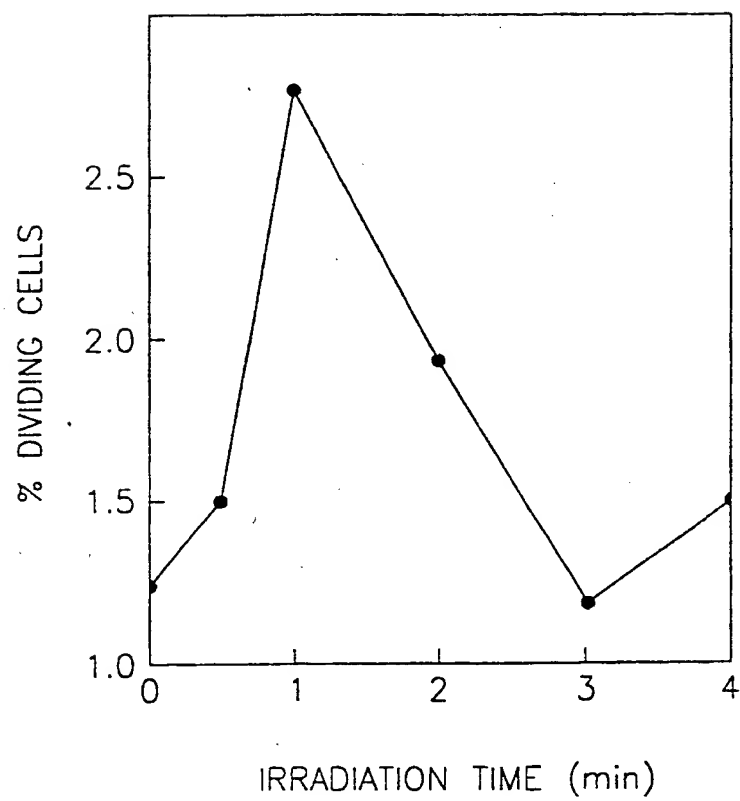


FIG.1

2/2

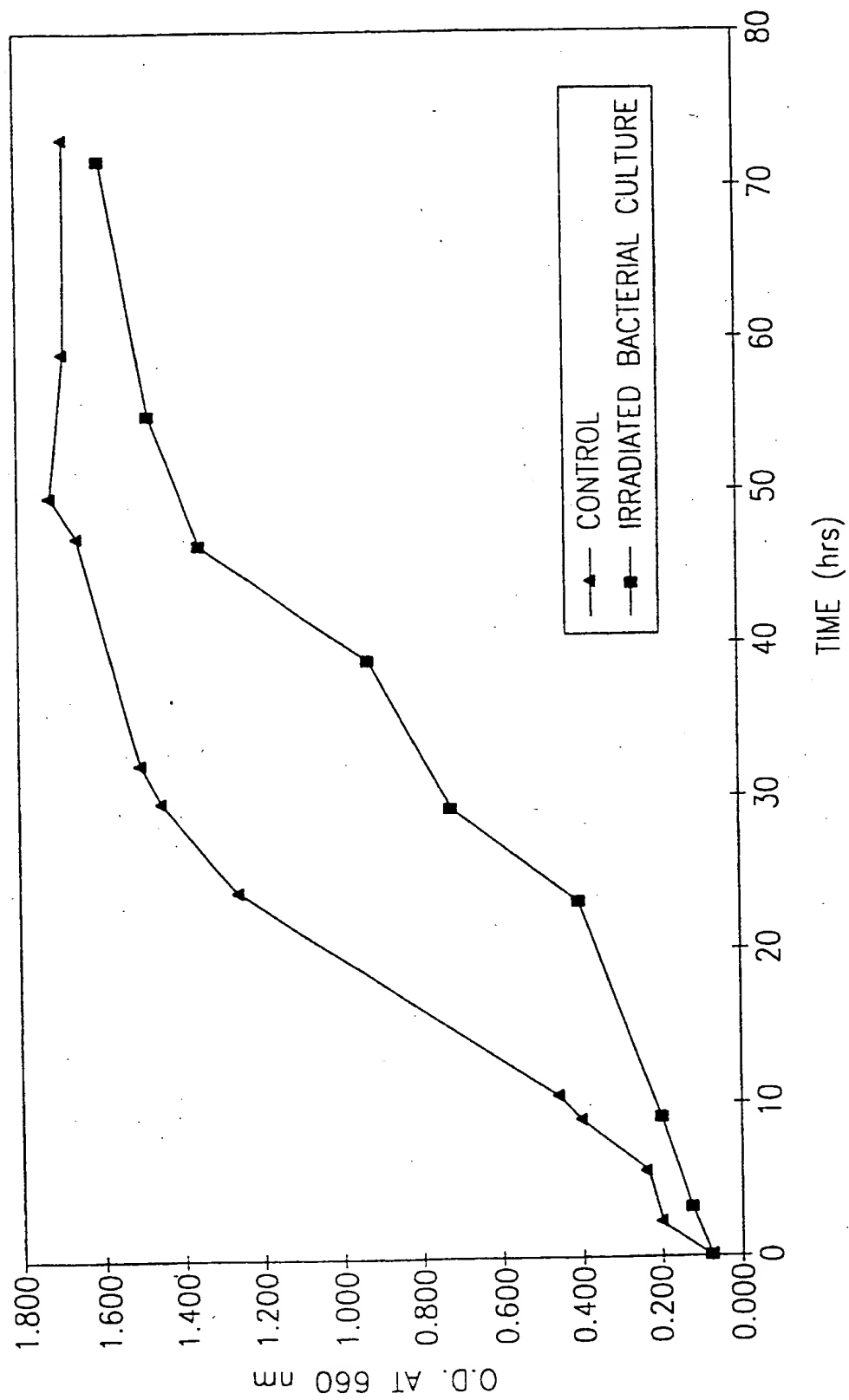


FIG.2

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/IL 97/00375

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61N5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|------------------------------------------------------------------------------------|-----------------------|
| X | WO 89 08474 A (ALLERGAN) 21 September 1989 | 10 |
| Y | see abstract | 11-13 |
| | see page 8 | |
| | see page 14; claims 17,31 | |
| | see the whole document | |
| | --- | |
| Y | WO 95 19810 A (BIOLIGHT PATENT HOLDING AB) 27 July 1995 | 11 |
| | see abstract; figure 2 | |
| | see page 3, line 6 - line 24 | |
| | --- | |
| Y | WO 91 13652 A (CANDELA LASER CORPORATION) 19 September 1991 | 12,13 |
| | see abstract | |
| | see page 18, line 22 - page 20, line 9 | |
| | --- | |
| | -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 February 1998

Date of mailing of the international search report

23.02.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Taccoen, J-F

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 97/00375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A | <p>LUBART, WOLLMAN, FROIEDMAN: "Effects on visible and near IR lasers on cell cultures"</p> <p>J. PHOTOCHEM. PHOTOBIOLOG. B. BIOL..</p> <p>vol. 12, 1 January 1992,</p> <p>pages 305-311, XP002054370</p> <p>cited in the application</p> <p>-----</p> | 10-14 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 97/00375

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:
Therapeutical method.(Rule 39.1(4))PCT.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 97/00375

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| WO 8908474 A | 21-09-89 | US 4966577 A AU 3430689 A | 30-10-90 05-10-89 |
| WO 9519810 A | 27-07-95 | SE 504298 C SE 502784 C AU 1549495 A AU 1549595 A CA 2181345 A CA 2181346 A CN 1138830 A CN 1138831 A EP 0740567 A EP 0740568 A JP 9508031 T JP 9508032 T SE 9400153 A SE 9402679 A WO 9519809 A | 23-12-96 15-01-96 08-08-95 08-08-95 27-07-95 27-07-95 25-12-96 25-12-96 06-11-96 06-11-96 19-08-97 19-08-97 21-07-95 21-07-95 27-07-95 |
| WO 9113652 A | 19-09-91 | AU 7463991 A AU 7562591 A DE 69103409 D DE 69103409 T EP 0519964 A WO 9113653 A US 5312395 A | 10-10-91 10-10-91 15-09-94 23-03-95 30-12-92 19-09-91 17-05-94 |

THIS PAGE BLANK (USPTO)